AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 13: Pulmonary Disease, Including Asthma

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U.S. Department of Health and Human Services
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www.ahrq.gov

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Prepared by:
ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

Richard Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Contents

Figures

Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 16,200 leads about potential topics has resulted in identification and tracking of about 1,900 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 500 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the five topics for which (1) preliminary phase III data on drugs, phase II or III data on devices and procedures were available, or programs were being piloted; (2) information was compiled before October 27, 2013, in this priority area; and (3) we received six to nine sets of comments from experts between April 19, 2012, and October 29, 2013. (Seventeen topics in this priority area were being tracked in the system as of October 29, 2013.) We present summaries on three topics (indicated below by an asterisk) that emerged as having high-impact potential on the basis of experts' comments, two of which were in the June 2013 Potential High-Impact Interventions report and one of which is new in this report. The material in this Executive Summary and report is organized alphabetically by intervention. Readers are encouraged to read the detailed information on these interventions that follows the Executive Summary.

Priority Area 13: Pulmonary Disease, Including Asthma

Topic	High-Impact Potential
1. * Ivacaftor (Kalydeco) for treatment of cystic fibrosis in patients with G551D-*CFTR* mutation	Moderately high
2. * Off-label azithromycin for prevention of chronic obstructive pulmonary disease exacerbations	Lower end of the high-impact-potential range
3. Off-label thalidomide for treating cough associated with idiopathic pulmonary fibrosis	No high-impact potential at this time
4. * Portable warm blood perfusion system (Organ Care System) for lung transplantation	High
5. School-based preventive asthma care technology (SB-PACT) program for management of asthma in school children	No high-impact potential at this time

Discussion

Pulmonary disease is a priority area in which relatively few interventions have been identified as meeting criteria for tracking in the AHRQ Healthcare Horizon Scanning System, despite extensive scanning. Experts deemed three topics as having high-impact potential: a new disease-modifying drug targeted at one of the genetic mutations seen in patients with cystic fibrosis (CF); an

off-label daily use of the antibiotic azithromycin to prevent chronic obstructive pulmonary disease (COPD) exacerbations; and a novel portable warm-blood perfusion system for lung transplantation.

Two additional topics were considered for inclusion in this report; however, they were deemed to have no high-impact potential at this time. One of these, thalidomide, has been investigated in a phase III trial for off-label use to treat cough associated with idiopathic pulmonary fibrosis. Thalidomide has been linked to safety concerns surrounding its use in women of reproductive age and experts commenting on the topic did not think the benefits reported in its phase III trials outweighed the associated risks. A second topic, a program—school-based preventative asthma care technology (SB-PACT)—is being evaluated for managing asthma in school children. However, experts were concerned about the sustainability of the program, run by school nurses, in light of education funding scarcities. Since expert comments, the program has received funding from the Institute for Healthcare Improvement (IHI). This program's high-impact potential will be reevaluated after results of the IHI-funded trial are released.

Ivacaftor (Kalydeco) for Treatment of Cystic Fibrosis in Patients with G551D-*CFTR* Mutation

- **Key Facts:** Before U.S. Food and Drug Administration (FDA) approval of ivacaftor, CF therapies had improved median survival times, but patients still had a shorter-than-normal life expectancy and required extensive treatment over a lifetime to maintain their health as well as possible. An unmet need has existed for novel, effective therapies to improve outcomes in this patient population. One new therapy now addresses the need in a very small proportion of the CF population; the remainder of the CF population still has only suboptimal therapy choices. The oral tablet ivacaftor (Kalydeco™, Vertex Pharmaceuticals, Inc., Cambridge, MA) targets the defective CF transmembrane conductance regulator (CFTR) protein that causes CF. The drug is intended as a first-line treatment for patients with the G551D-*CFTR* mutation—about 4% of patients with CF. Ivacaftor tablets are indicated for oral administration, one 150 mg dose every 12 hours for patients 6 years of age or older. Several phase III trials have been cosponsored by the Cystic Fibrosis Foundation, of Bethesda, MD. In trials, effects on pulmonary function were reported as early as 2 weeks, and a statistically significant treatment effect was reported to be maintained through week 48. Also through week 48, investigators reported, patients given ivacaftor were 55% less likely to have a pulmonary exacerbation than were patients given placebo. Ivacaftor is also being evaluated in 10 other *CFTR* gene mutations known to cause CF, which could expand the indicated patient population. In January 2012, FDA approved ivacaftor for treating patients aged 6 years or older who have a G551D mutation in the *CFTR* gene. As of November 2013, a U.S.-based, online aggregator of prescription drug prices listed prices for the drug at about $27,000 per month, which totals about $324,000 annually. Vertex offers patient information about assistance programs to help them afford the therapy. Health insurance plans providing coverage require prior authorization, which includes confirmation of the mutation, and copayment levels vary according to the patient's coverage level. To renew prescription coverage after an initial authorization, many plans require evidence of patient response to treatment. In October 2013, *JAMA* published an editorial (by O'Sullivan and colleagues) on orphan-drug pricing, indicating that pricing models are unsustainable and using Kalydeco as an example. The editorialists wrote, "A model of reduced profitability, particularly for lifelong therapies, is ethically responsible and institutionally plausible but will require pharmaceutical companies to develop new models and educate investors about the long-term advantage of regaining the trust of the public."

- **Key Expert Comments:** Overall, experts commenting on this topic thought that this drug could meet the need for a novel, effective, oral treatment for appropriately selected CF patients. This view was tempered, however, by the fact that the drug is intended only for the approximate 4% of patients who have this mutation. Experts thought that this drug would affect current care processes and patient management by offering patients a convenient oral therapy to directly treat CF's cause, which could reduce the need for intravenous treatments, ventilation therapy, and chest physiotherapy, if the drug halts disease progression. At the time experts offered their opinions, the annual ivacaftor cost was estimated at $294,000. Experts identified cost as a significant and potentially controversial issue because even for patients with prescription drug coverage, copayments are significant.
- **Potential for High Impact:** Moderately high

Off-Label Azithromycin for Prevention of Chronic Obstructive Pulmonary Disease Exacerbations

- **Key Facts:** COPD is the third most common cause of death and chronic complications in the United States. Acute COPD exacerbations dramatically change the disease course and are associated with a rapid decline in patients' lung function and worsening quality of life. Better treatments to prevent COPD exacerbations are needed. Although antibiotic therapy is often given during an exacerbation, published clinical guidelines have recommended it not be used ongoing to prevent future exacerbations. However, a recent study on azithromycin use to prevent exacerbations has garnered new interest in prophylactic COPD therapy. Results of a randomized controlled trial (RCT) on prophylactic azithromycin for COPD exacerbations were published in 2011 in the *New England Journal of Medicine*. Azithromycin (Zithromax®, Pfizer, Inc., New York, NY), is a macrolide antibiotic with broad-spectrum activity that binds to the 50S ribosomal subunit of susceptible bacteria, interfering with microbial protein synthesis. Macrolide antibiotics are also purported to have anti-inflammatory properties, which could play a role in preventing COPD exacerbations. Azithromycin is being evaluated for off-label use to prevent COPD exacerbations and slow disease progression in patients who continue to have acute exacerbations despite receiving standard care. The drug has been administered orally, at a dosage of 250 mg once daily for this purpose. In May 2002, FDA approved azithromycin for treating acute bacterial COPD exacerbations due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* infection. Azithromycin is not approved for prophylaxis of COPD exacerbations in patients at elevated risk but could be used off label in this patient population.

  In the RCT, patients with COPD (n=1,577) at increased risk of exacerbations received azithromycin 250 mg daily or placebo for 1 year in addition to standard care to determine whether daily azithromycin could reduce the frequency of COPD exacerbations. Patients treated with the drug were reported to have a longer median time to the first exacerbation (266 days vs. 174 days) and less-frequent exacerbations than patients treated with placebo. Adverse events associated with azithromycin included hearing loss and cardiac arrhythmias and concerns about antibiotic-resistance with daily use.
- **Key Expert Comments:** Overall, experts commenting on this intervention stated that daily prophylactic azithromycin has the potential to reduce the rate of exacerbations in patients with COPD. Slowing disease progression could lead to improved quality of life and reduced costs. However, a number of triggers for COPD exacerbations exist, and the patient subpopulations in which azithromycin could be most effective remain poorly understood.

Azithromycin is not expected to replace treatment but to be additive to COPD treatment options. Experts commenting on this topic thought azithromycin would minimally disrupt patient management while potentially reducing the incidence of serious complications. They did, however, express concern about antibiotic resistance with ongoing daily use.

- **Potential for High Impact:** Low

Portable Warm Blood Perfusion System (Organ Care System) for Lung Transplantation

- **Key Facts:** Current methods of donor organ preservation expose the organ to sustained periods of ischemia and hypothermia, which can result in organ damage that can make an organ unsuitable for transplantation. The Organ Care System for lung preservation (OCS Lung) is in development by TransMedics, Inc. (Andover, MA). The OCS Lung is a portable, ex-vivo, warm blood perfusion, ventilation, and monitoring system that purportedly maintains the donor lungs in a "near physiologic state," potentially optimizing organ health and allowing for continuous evaluation during transport. The company calls it a "living organ" transplant. The OCS Lung consists of a portable, battery-operated console with a wireless monitor, a perfusion module described by the manufacturer as a "transparent, sterile chamber designed to protect the organ and maintain the appropriate, warm temperature and humidity," and a solution set to deliver nutrients to the preserved donor lungs. In pilot trials, the OCS Lung console was connected to the donor lung via the pulmonary artery and the trachea. Blood is delivered through the pulmonary artery and drains directly into the perfusion module chamber. A ventilator delivers air to the lungs via the trachea. Donor lungs are perfused with a solution enriched with two red blood cell concentrates that are matched to the intended transplant recipient. With the OCS, clinicians can measure the oxygen concentration in the blood to assess lung function. OCS Lung may also improve donor lung condition so that lungs previously considered as marginal in quality are transplantable. This would increase the number of viable organs for transplantation. Furthermore, by replacing static hypothermic storage with active perfusion, the technology is said to reduce organ-damaging cold ischemic time (particularly during transport from donor to recipient). This potentially increases the time an organ can be maintained outside the body before transplantation. The OCS is also in trials for preserving donor hearts. The OCS Lung is an investigational device, not yet approved by FDA. If approved, it would be the first portable, warm-blood perfusion system for donor lung organ preservation.
- **Key Expert Comments:** Experts commented that the unmet need is great for increasing the number and quality of transplantable donor lungs. They generally agreed that the potential of this intervention is high to increase the pool of viable lungs and increase the quality of transplanted lungs. Experts expressed enthusiasm about provider and patient acceptance of this technology. Experts also noted the potential for the OCS Lung to reduce transplant-associated complications and adverse events. Some experts thought the OCS Lung could alleviate the intensity and complexity of overall treatment after transplantation. Some experts did not think the OCS Lung would affect health disparities; however, others suggested the high costs associated of acquiring the OSC Lung equipment and access to health care coverage for organ transplantation by health disparate groups could further contribute to health disparities.
- **Potential for High Impact:** High

Pulmonary Disease, Including Asthma, Interventions

Ivacaftor (Kalydeco) for Treatment of Cystic Fibrosis in Patients with G551D-*CFTR* Mutation

Unmet need: Current therapies for cystic fibrosis (CF) have improved predicted median survival, but patients with CF still have a shorter-than-normal life expectancy and require extensive treatment over a lifetime to maintain good health as much as possible. Thus, an unmet need has existed for novel, effective medications to improve outcomes in this patient population.

Intervention: Ivacaftor (Kalydeco™) is a small-molecule, CF transmembrane conductance regulator (CFTR) modulator that improves the function of the *CFTR* gene by increasing CFTR activity in transporting negatively charged chloride ions across cell membranes to the cell surface, improving hydration and clearing mucus in patients with CF.[1,2] Ivacaftor also promotes functional activity for two other *CFTR* mutations (i.e., F508del, R117H) and has some effect on the wild-type *CFTR* gene. Ivacaftor targets the defective protein that causes CF and is intended as a first-line treatment for the 4% of patients with CF who have the G551D mutation.[3] Ivacaftor is administered at a dosage of 150 mg twice daily with fat-containing food in patients 6 years of age or older.[4]

Clinical trials: Ivacaftor, approved by the U.S. Food and Drug Administration (FDA) in 2012, continues to be under study in a phase II trial and a phase III trial.[5,6] In a randomized, double-blind, placebo-controlled, phase III trial, cosponsored by the Cystic Fibrosis Foundation, of Bethesda, MD, and the drug manufacturer, patients (n=161) with at least one copy of CF mutation G551D given ivacaftor had a predicted forced expiratory volume in 1 second (FEV_1) measurement that was 10.6 percentage points higher than patients treated with placebo through week 24 ($p<0.001$).[7] Effects on pulmonary function were observed as early as 2 weeks, and a significant treatment effect was maintained through week 48. Also through week 48, patients given ivacaftor were 55% less likely to have a pulmonary exacerbation than were patients given placebo ($p<0.001$). Patients treated with ivacaftor also demonstrated a significant improvement in quality of life ($p<0.001$). By 48 weeks, patients treated with ivacaftor had gained significantly more weight and secreted significantly less chloride in sweat samples, a key indicator of CFTR activity ($p<0.001$ for both measures). The incidence of adverse events was similar with ivacaftor and placebo, with a lower proportion of serious adverse events with ivacaftor than with placebo (24% vs. 42%).[7] Long-term study results became available in September 2013; however, these data were not available at the time of expert comment. Data were reported from 192 patients (144 adults, 48 children) in an open-label extension of completed ivacaftor trials at week 144 of treatment.[8] As reported by study authors, "Patients treated with ivacaftor had sustained improvements in FEV_1 and weight up to 144 weeks of treatment. Among the adolescents/adults who received placebo in STRIVE [the earlier, 48-week trial], time to first exacerbation in PERSIST [the 96-week extension study] was similar to that seen in patients who had received ivacaftor in STRIVE. In the adult/adolescent group, the decrease in exacerbation rate compared with the prior placebo rate was maintained up to 144 weeks of treatment. SAEs [serious adverse events] were reported in 30 (20.8%) adults and 8 (16.7%) children during the first 48 weeks of PERSIST and in 34 (23.6%) adults and 10 (20.8%) children during the subsequent 48 weeks. Two adults and one child discontinued due to an AE (depression, adrenal insufficiency, and ALT elevation)."[8]

Manufacturer and regulatory status: Vertex Pharmaceuticals, Inc., of Cambridge, MA, makes ivacaftor. In January 2012, FDA approved ivacaftor for treating patients aged 6 years or older who have a G551D mutation in the *CFTR* gene.[9]

Diffusion: Sales projections for ivacaftor have slightly exceeded the company's and industry analysts' projections through the third quarter of 2013, despite the orphan drug's high cost.[10] Based on a November 2013 query of a U.S.-based, online aggregator of prescription drug prices, ivacaftor cost ranged between $27,046 and $27,850 for a monthly supply.[11] The manufacturer has implemented

stratified pricing that is based on patient insurance status and income, to improve access.[12] (This latest cost and coverage information was not available at the time we received expert comments. The information available to experts was an estimated cost of $294,000 per patient per year, and coverage policies had not been established at some payers.) Vertex also offers patient information about assistance programs to help patients afford the therapy. Although ivacaftor's price is considered to be the highest-cost drug therapy on the market today, the company indicated it set pricing on the basis of conversations with patients, physicians, and payers.[13] In October 2013, *JAMA* published an editorial (O'Sullivan and colleagues) on orphan-drug pricing, indicating that pricing models are unsustainable and using Kalydeco as an example.[14] The editorialists wrote, "A model of reduced profitability, particularly for lifelong therapies, is ethically responsible and institutionally plausible but will require pharmaceutical companies to develop new models and educate investors about the long-term advantage of regaining the trust of the public."

Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found all had policies that include coverage. Generally, health plans require preauthorization and renewal authorization, including confirmation of gene mutation status and confirmation that the drug is working (when renewal request is made).[15-25]

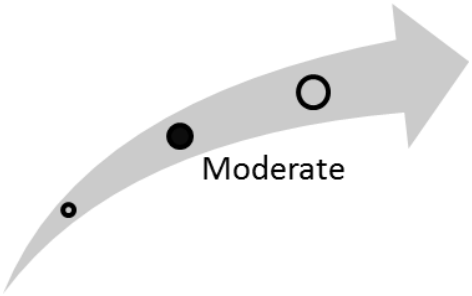
Ivacaftor in combination with another experimental CF drug, lumacaftor, has also been shown to improve lung function in patients with CF who have two copies of the *CFTR*-F508del mutation, according to recent, phase II trial results.[26] The F508del mutation is the most common CF mutation; about 90% of patients with CF are heterozygous for F508del in North America, and about 50% of patients are homozygous.[26]

Additionally, the manufacturer is sponsoring a study to evaluate ivacaftor's efficacy in patients with CF caused by other known mutations including the following: R117H, G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D.[27,28] Thus, ivacaftor may gain a broader patient indication in the future.

Clinical Pathway at Point of This Intervention

Patients with CF often require chronic use of inhaled, intravenous, or oral antibiotics to prevent or treat acute infections in lungs already weakened by disease. They also use inhaled medications, ventilators, and chest physiotherapy singly or in combination to help release the CF-associated, thick mucus that damages lung tissue over time. Lung transplantation can reduce the effects of CF for some individuals.[29] As the disease progresses, some patients require mechanical breathing support, especially while sleeping. Ivacaftor is intended as a first-line treatment for patients with CF who have the G551D-*CFTR* mutation, and it can be used in conjunction with any of the other therapies as needed.

Figure 1. Overall high-impact potential: ivacaftor (Kalydeco) for treatment of cystic fibrosis in patients with G551D-*CFTR* mutation



Overall, experts commenting on this intervention expressed some confidence that this drug has potential to meet the need for a novel CF treatment that can improve health outcomes, although this view was tempered by the fact that CF is relatively rare and within this population, ivacaftor is intended for only the 4% of patients with the G551D-CFTR mutation. Because the drug is intended to be delivered orally, it could reduce the need for visits to health care facilities for regular oxygen, chest, and intravenous therapies. However, because of the small patient population and the drug's oral administration, ivacaftor is not expected to have a major impact on health care processes such as staffing or infrastructure requirements; thus, the experts expected it could be easily adopted. The high annual cost of ivacaftor therapy was identified as a potentially controversial issue. Although experts thought that insurance coverage would help reduce some patients' out-of-pocket costs, they also noted that copayments might be high for this specialty pharmaceutical. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, or health systems backgrounds, offered perspectives on this intervention.[30-35] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need for novel treatments for CF is important, particularly if those treatments are disease-modifying instead of merely palliative, the experts generally agreed. However, they stated that the importance of this unmet need is tempered by the fact that CF is a rare condition and that within the small population affected by CF, 96% of patients would be ineligible for this treatment.

Ivacaftor appears to have a sound theory underlying its mechanism of action and potential to improve patient outcomes, the experts said, basing their opinions on positive trial results. However, one health systems expert noted that additional clinical trials evaluating quality of life should be performed to better evaluate the drug's impact.

The experts stated that although the drug's price is quite high, it may have limited impact on costs overall because of the small number of patients eligible for this therapy. Additionally, the anticipated reductions in oxygen and chest therapy, hospitalizations, and other complications could offset costs in the long term. However, one expert representing a health systems perspective estimated that treating all eligible patients with ivacaftor would cost the health care system about $400 million annually, which the expert regarded as an unsustainable level for a disease that affects such a small population of patients.

Acceptance and adoption: Experts generally thought patient and clinical acceptance would be wide and rapid. Possible barriers to acceptance include issues that could arise from a patient's health insurance coverage and costs. Also, if physicians observe limited efficacy in clinical practice, they could hesitate to prescribe such an expensive drug.

Health care delivery infrastructure and patient management: Because the drug is an oral treatment and because of CF's rarity, experts providing comments did not think it would have a major impact on health care operations such as staffing and infrastructure needs. However, some experts suggested that it might reduce frequency of outpatient visits and inpatient care for flares and complications for patients with the mutation.

This drug could affect current care processes and patient management by offering patients a convenient oral therapy to directly treat CF's cause, the experts thought. A drug that halts disease progression could reduce the need for ventilation therapy, chest physiotherapy, and intravenous fluids, experts noted. Initiating therapy would necessitate clinicians spending time to explain to patients and their caregivers the advantages and limitations of the therapy and how it might affect care.

Health disparities: Ivacaftor could improve health disparities, one clinical expert noted, stating that rural patients and "working families" commonly have barriers to treatment when they must travel frequently to a care facility. If ivacaftor reduces exacerbations and complications, its convenience as an oral medication could improve health disparities.

Off-Label Azithromycin for Prevention of Chronic Obstructive Pulmonary Disease Exacerbations

Unmet need: Chronic obstructive pulmonary disease (COPD) is the third most common cause of death and chronic complications in the United States.[36] Acute COPD exacerbations dramatically change the disease course and are associated with a rapid decline in lung function and worsening quality of life. Better treatments to prevent COPD exacerbations are needed.[37]

Intervention: Azithromycin (Zithromax®), a broad-spectrum antibiotic, is in the azalide subclass of macrolide antibiotics.[38] Azithromycin binds to the 50S ribosomal subunit of susceptible bacteria, interfering with microbial protein synthesis.[38] Besides antimicrobial activity, macrolide antibiotics purportedly also have anti-inflammatory properties (against cytokines, chemokines, and other mediators, such as leukotriene B_4 and matrix metalloproteases),[39] which are thought to play a role in preventing COPD exacerbations and could position the drug as a useful adjunct to standard care.[36] Macrolide antibiotics also purportedly decrease expression of adhesion molecules that promote neutrophil accumulation in the lungs—neutrophils are a principal mediator of inflammation and tissue destruction.[39] Lastly, azithromycin is thought to improve airway clearance of apoptotic cells and bacteria, reducing secondary necrosis that occurs from release of cellular toxins that could contribute to inflammation.[40]

Azithromycin is being evaluated off label to prevent COPD exacerbations and slow disease progression. In trials, the drug has been given orally, 250 mg, once daily.[37] According to one published report, prophylactic azithromycin would be used in patients who continue to have acute exacerbations despite receiving standard care. Other patient-selection criteria for the treatment include having had at least two acute exacerbations the previous year as a baseline to assess treatment response and to limit overuse of azithromycin.[36]

Clinical trial: In a randomized controlled trial (RTC), patients with COPD who were at increased risk of exacerbations received azithromycin 250 mg daily (n=570) or placebo (n=572) for 1 year plus standard care to determine whether daily azithromycin reduced COPD exacerbations. The median time to first exacerbation was 266 days (95% confidence interval [CI], 227 to 313) among patients treated with azithromycin and 174 days (95% CI, 143 to 215) among patients receiving placebo ($p<0.001$). The frequency of exacerbations was 1.48 exacerbations per patient-year in the azithromycin group and 1.83 per patient-year in the placebo group ($p=0.01$). The hazard ratio for having an acute COPD exacerbation was 0.73 per patient-year (95% CI, 0.63 to 0.84) in the azithromycin group ($p<0.001$). Hearing decrements were more common in the azithromycin group than in the placebo group (25% vs. 20%, $p=0.04$).[37]

Common adverse events associated with azithromycin use include angioedema and cholestatic jaundice, which are potentially serious but were reported rarely.[38] In clinical trials, adverse events that were most associated with patients discontinuing treatment were nausea, vomiting, diarrhea, and abdominal pain.[38] Other adverse events associated with azithromycin that could dissuade a physician from prescribing it for prophylaxis in COPD patients include hearing loss and cardiac arrhythmias.[37,38] Additionally, investigators note concerns about development of antibiotic-resistant bacteria in patients treated with daily azithromycin.[37,41]

Manufacturer and regulatory status: Pfizer, Inc., of New York, NY, makes azithromycin. In May 2002, FDA granted marketing approval for azithromycin for treating acute bacterial COPD exacerbations due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* infection.[42] FDA has not approved azithromycin for prophylaxis of COPD exacerbations in patients at elevated risk; some researchers have explored use of the drug in this patient population, which is an off-label use.

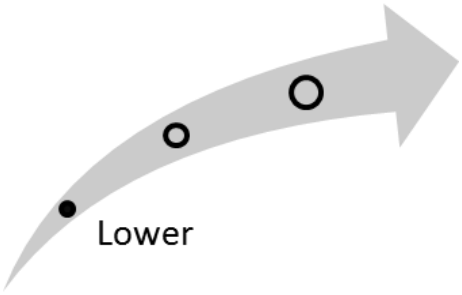
Diffusion: Ongoing prophylactic antibiotic use to reduce COPD exacerbations does not appear to have diffused widely because clinical guidelines have recommended against it, but those guidelines refer to evidence that predated the 2011 publication of new data from the RCT described above.[37]

Based on a November 2013 query of U.S.-based, online aggregator of prescription drug prices, a 1-month supply of azithromycin (generic) costs about $39, so the drug would be relatively inexpensive for long-term, prophylactic use.[43]

Clinical Pathway at Point of This Intervention

COPD treatment focuses on managing stable disease and exacerbations. Treatment includes smoking-cessation counseling and nicotine-addiction treatment, medications to address breathing issues (i.e., long-acting bronchodilators, inhaled glucocorticosteroids), and antibiotics for lung infections. Clinicians also recommend that patients with COPD receive annual flu vaccinations and a pneumococcal polysaccharide vaccination. None of these approaches halts disease progression. In cases of advanced disease, supplemental oxygen or surgery (i.e., lung volume reduction, lung transplantation) may be recommended.[44] Azithromycin has been proposed as prophylactic, ongoing therapy to reduce the frequency of disease exacerbations, which may slow disease progression.

Figure 2. Overall high-impact potential: off-label azithromycin for prevention of chronic obstructive pulmonary disease exacerbations



Overall, experts commenting on this intervention stated that daily prophylactic azithromycin has potential to reduce the rate of exacerbations in patients with COPD. Slowed disease progression could lead to improved patient quality of life and reduced costs. However, a number of triggers for COPD exacerbations exist, and the patient subpopulations for which azithromycin would be most effective remain poorly understood. Prophylactic azithromycin, if used, would be added current COPD treatment and would not disrupt daily patient management. Some experts expressed concern about antibiotic resistance. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, or health systems backgrounds, offered perspectives on this intervention.[45-50] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: No cure exists for COPD, the third leading cause of death and a significant source of health care costs, the experts stated. COPD exacerbations can lead to significant declines in lung function and progression towards respiratory failure. Daily prophylactic use of azithromycin seems to be a promising treatment to slow COPD progression, the experts stated. However, one expert cautioned that many COPD exacerbations have no identifiable cause and many mild to moderate exacerbations may go unreported, complicating analysis of azithromycin's impact.

Acceptance and adoption: Clinicians might readily accept azithromycin as a simple, noninvasive, and affordable treatment to prevent exacerbations and slow COPD progression, with some caveats, noted the experts. Some experts stated that risk of hearing loss, cardiac arrhythmias, and antibiotic resistance are factors that would make some physicians reluctant to prescribe the antibiotic. The experts also stated patients would be generally accepting of a simple, relatively low-cost treatment regimen that could prevent their quality of life from declining.

Health care delivery infrastructure and patient management: If azithromycin is effective in preventing COPD exacerbations, reductions in pulmonary, acute, long-term, and intensive care units could be realized, the experts theorized. Although the cost of azithromycin therapy would be added to current treatment costs, its low cost and its potential to offset costs of complications were seen by some experts as having a neutral or perhaps even cost-saving impact.

Portable Warm Blood Perfusion System (Organ Care System) for Lung Transplantation

Unmet need: In 2012, 28,051 people received organ transplants (about 79 per day); however, because of a shortage of donated organs, an average of 18 people die each day while waiting for a donor organ.[51] The process of organ transplantation from donor to recipient can alter organ homeostasis and affect both the speed at which and degree to which normal organ function returns.[52] Current methods of organ preservation expose the organ to sustained periods of ischemia and hypothermia, which can damage donor organs.[52,53] Only about 10% to 30% of donated lungs are considered to be suitable for transplantation,[53] and in 10% to 20% of patients who have undergone lung transplantation, donor lungs have been so severely damaged by the time of transplantation that the patient requires additional supportive therapies (i.e., ventilation, pharmacologic interventions).[54] The development of new strategies to better preserve or improve donor-lung quality could affect the number of lungs available for transplantation.[53]

Intervention: The Organ Care System (OCS) Lung is an integrated and portable ex-vivo lung perfusion system intended to assess and improve marginal lungs and potentially to preserve or improve the condition of routine donor lungs. The system's potential advantages over conventional organ preservation methods include immediate and sustained donor lung recruitment at the donor site; reduced time for the organ to be maintained in a cold ischemic state, especially during transport; and continuous organ-quality assessment during transport from donor to recipient.[54] Furthermore, the system can potentially increase the time an organ is maintained outside the body in good condition before transplantation.[55] The company calls this a "living organ" transplant.

The OCS Lung preservation system consists of a portable, battery-operated console with a wireless monitor, a perfusion module described by the manufacturer as a "transparent, sterile chamber designed to protect the organ and maintain the appropriate, warm temperature and humidity," and solution set to deliver nutrients to the preserved donor lungs. The central platform component is the perfusion module chamber that protects and maintains the lungs. The platform also includes an oxygen supply, ventilator, and a blood pump. The monitor controls the platform and provides information that enables assessment of the donor organ.[55,56]

In pilot trials, the harvested lung was connected to the OCS Lung by means of the pulmonary artery and trachea. Blood is delivered through the pulmonary artery and drains directly into the perfusion module chamber. A ventilator delivers air to the lungs via the trachea. Donor lungs are perfused with a solution (Steen solution, Vitrolife AB, Göteborg, Sweden) that is enriched with two red blood cell concentrates, which are matched to the transplant recipient. The enriched solution is also supplemented with other compounds, including cefazolin, ciprofloxacin, voriconazole, methylprednisolone, glucose, multivitamins, and THAM buffer.[55]

While donor lungs are undergoing warm perfusion and ventilation in the OCS system, clinicians can assess the donor lung's functional capacity by measuring the oxygen concentration in the blood. Once on-site for transplantation, warm blood perfusion is stopped, and the lungs are cooled using a heat exchanger or cold flush perfusion. After the lungs are immersed in cold low-potassium solution, transplantation may begin.[55]

Clinical trials: Two trials of the OCS Lung have been completed, and one phase III trial is ongoing and has reported preliminary data. One trial investigated the OCS Lung's feasibility for lung preservation during lung transplantation.[55] The study authors reported, "All grafts and patients (n=12) survived to 30 days; all recipients recovered and were discharged from hospital." A second trial investigates tissue alteration in donor lungs preserved with the OCS Lung compared with standard care.[57] As reported by study authors, "No significant morphological difference were observed in terms

of: intraalveolar edema, capillary congestion, and intraalveolar hemorrhage. OCS lung donors showed less leucocyte margination and significant less apoptosis both at cold ischemia time and after reperfusion."[57] Preliminary results from the phase III, INSPIRE trial have been reported in a press release from the manufacturer, stating: "The donor lungs preserved using the OCS Lung technology had significantly lower incident of severe primary graft dysfunction grade 3 (PGD3) after lung transplantation as compared to lungs that were preserved using cold storage. In addition, other important clinical parameters like in-hospital mortality, six months survival, rate of lung related complications, time on mechanical ventilation and ICU [intensive care unit] time were better in the OCS group as compared to cold storage."[58]

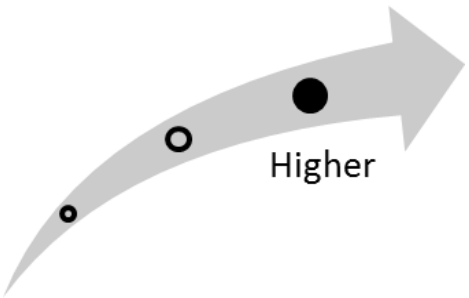
Manufacturer and regulatory status: The OCS Lung is being developed by TransMedics, Inc. (Andover, MA), for donor organ preservation during lung transplantation.[59] The OCS is also in clinical trials for donor heart preservation. As an investigational device, OCS Lung is not yet approved by FDA. In January 2011, the OCS Lung received a Conformité Européene (CE) mark and is in use in Europe.[55] If approved by FDA, the OCS Lung would be the only portable, warm-blood perfusion system available in the United States for donor lung preservation.

Diffusion: The system is in the innovative phase in the United States. If approved, use of the system would be part of the bundled payment for organ harvesting and transplantation. The manufacturer has not provided any information about the cost of the OCS Lung. One report indicated that hospitals in Europe pay about $60,000 for each machine.[60]

Clinical Pathway at Point of This Intervention

The standard method for preserving donor lungs for transplantation is cold flush and static cold storage.[55] This method has traditionally been successful for high-quality donor organs when the ischemia times are not excessive.[55] At the onset of the cold-storage process, the lungs are flushed with a cold solution in an anterograde and retrograde manner to clear the blood from the organ and to ensure proper reperfusion upon transplantation.[61,62] After flushing, the lungs are cooled and stored between 4 and 8 °C to reduce the metabolic rate and slow the degeneration process.[62] Inflated donor lungs are considered to be optimal; collapsed lungs do not tolerate ischemia very well. Lung inflation is done with an inspired oxygen tension of 30% to 50%.[61] The donor lungs are immersed in additional cold preservation solution and placed on ice for transport.[62] The total ischemic time is generally less than 8 hours.[61] The OCS Lung system would replace this method if approved for marketing and adopted.[63]

Figure 3. Overall high-impact potential: portable warm blood perfusion system (Organ Care System) for lung transplantation



Experts commented that the unmet need is great for more, higher-quality, transplantable donor lungs and generally agreed that this intervention has high potential to increase the pool and quality of viable donor lungs. Experts were optimistic about both provider and patient acceptance of this technology. Experts also noted the potential for the OCS Lung to reduce transplantation-associated complications

and adverse events. Some experts anticipated the OCS Lung could alleviate the intensity and complexity of overall treatment after transplantation. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, or health systems backgrounds, offered perspectives on this intervention.[64-70] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The majority of experts agreed that a substantial unmet need exists for more and higher-quality, transplantable donor lungs and that this intervention could address that need. However one expert expressed this caveat about the demand for donor lungs: "[It] is much lower than the demand for kidneys and livers."[65] Experts noted that the purported increased quality in lung tissue could result in better health outcomes for patients; however, experts called for more safety and efficacy data, as well as long-term efficacy data, to support this claim.

Acceptance and adoption: Clinician acceptance and adoption of the system is expected to be high, according to the experts. Two experts, one with a research perspective and one with a clinical perspective, anticipated that adoption of the OCS Lung would be contingent on a cost-benefit analysis showing that the system improves outcomes over the current standard methods of donor organ preservation.[64,67] Patients are expected to readily accept the OCS Lung because of the purported impacts of improved donor-lung quality and improved health outcomes, experts remarked.

Health care delivery infrastructure and patient management: The majority of experts suggested the OCS Lung could potentially reduce transplantation-associated complications and adverse events. Experts thought patient length of stay and staff needed for treating transplant complications could be significantly reduced with widespread use of the OCS Lung if it truly improves lung quality. Some experts remarked on a possible learning curve for widespread use of the OCS Lung, highlighting the training required to properly operate the system. In terms of patient management, experts concluded the potential for increased availability of lungs for transplantation could cause a small disruption. Furthermore, the potential exists for altering the current standard practices for lung transplantation, in both harvesting and implanting donor lungs, experts noted. Some experts anticipated the OCS Lung could alleviate the intensity and complexity of overall treatment after transplantation.

The OCS Lung would significantly increase health care costs for lung transplantation, experts concluded. However, experts anticipated the increased cost associated with purchase of the OCS Lung would eventually be offset by increased revenue from preserving and transplanting more lungs and decreased costs from shorter lengths of stay and reduced complications.

Health disparities: Experts were divided on the impact of the OCS Lung on health disparities. Some experts did not think health disparities would be affected at all. Other experts felt that the high costs associated with the OCS and the limited access to health care coverage in health disparate populations would further contribute to disparities in health.

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